REMARKS

By a Final Office Action dated March 19, 2007, the Examiner in charge of this case rejected the claims of this application on a variety of grounds. Claims 1-29 are currently pending in the application; Claims 16-18 and 25-27 are withdrawn from consideration as drawn to a non-elected invention; and Claims 1-2, 7-10, 12-15, and 19-21, 23 and 24 are rejected under 35 U.S.C. 103(a). Claim 22 is objected to, but would be allowable if rewritten in independent form. Claims 28 and 29 are allowable. Based on this submission, applicants respectfully request reconsideration and withdrawal of all the rejections set forth in the Office Action.

Claim Amendments

Claims 1 and 19 are amended to affirmatively recite "in the presence of a donor-molecule". Claim 9 is amended to depend from Claim 1. As suggested by the Examiner, Claim 19 was amended to include the limitation of Claim 22.

New Claim 30 mirrors Claim 19 and includes the fluorescence resonance energy transfer detection method. New Claim 31 mirrors Claim 1 and refers to specific enzymes of the group transfer reaction and Claim 32-33 are drawn to enzyme species for group transfer reactions. In view of the remarks provided herein below, it is believed that the cited documents do not disclose a species falling within the claimed genus (see MPEP 2131.02). Thus, a generic claim should be allowed.

Support for these claim amendments is found for example, throughout the specification, specifically at orginal Claims 9, and 11 pg. 1, ¶ 5, pg. 2, ¶7 to pg. 5, ¶16; pg. 6, ¶18; pg. 7, ¶¶ 19-21; pg. 11, ¶50 to pg. 12, ¶ 61. No new matter is added by the introduction of these claims.

Claim Rejections 35 USC §103

The Examiner previously rejected Claims 1-2, 7-10, 12-15, 19-21, 23, and 24 under USC 103(a) based on Seethala (2000) in view of either Li et al. or Glassler (2001). Upon amending Claim 1, this rejection was overcome. The Examiner has now cited new rejections for the same claims, as well as Claims 5, 6 and 11 based on Seethala (2000) in view of either Li et al. or Glassler (2001), and additionally, Bredehorst.

The Examiner asserts that Bredehorst "does not teach or fairly suggest the detection of the donor product ADP by an antibody specific to ADP in the presence of the donor ATP" (See pg. 12 of 3/19/07 Office Action). Rather, it teaches production of antibodies to ADP-ribose and AMP, and how design of the immunogen can lead to desired specificity for AMP. The Examiner also asserts that Bredehorst teaches "an antibody which recognizes 5'-AMP a nucleotide and a donor product through a relative binding affinity of 100, and does not recognize 5'-ADP the donor molecule by virtue of a weak relative binding affinity of 1.6" (See pg. 5 of 3/19/07 Office Action).

We acknowledge that Bredehorst teaches production of antibodies to AMP and perhaps even to ADP-ribose; however, neither is a donor product of a group transfer reaction. Thus, this alleged teaching has no relevance to the claims at issue. In this regard, any conclusions drawn from Bredehorst on "how design of the immunogen can lead to desired specificity for AMP" are (1) irrelevant and (2) cannot be applied to design an immunogen to the donor product, ADP.

Bredehorst, et al. describes a largely unsuccessful attempt to produce antibodies to ADP-ribose using an ADP-ribose antigen, which yielded primarily antibodies to AMP (see Figure 1). Bredehorst hypothesizes that the ADP-ribose hapten is cleaved by endogenous enzymes in the rabbit, to produce AMP. Indeed, Bredehorst et al. provides

> "[H]owever, in this and all other cases, primarily antibodies directed against 5'-AMP were obtained. This may be explained at least in part by the instability of the pyrophosphate bond of the ADP-ribose haptens in the recipient animals" [see, pg. 112, 1st paragraph].

Thus, applicants acknowledge that Bredehorst et al. provides sufficient teaching for production of antibodies recognizing AMP preferentially over ADP. However, the conclusion that Bredehorst teaches development of antibodies to ADP-ribose is uncertain, since according to Table 5 of Bredehorst, the "best" antibody recognized AMP at a rate that was more than two-fold stronger than ADP-ribose.

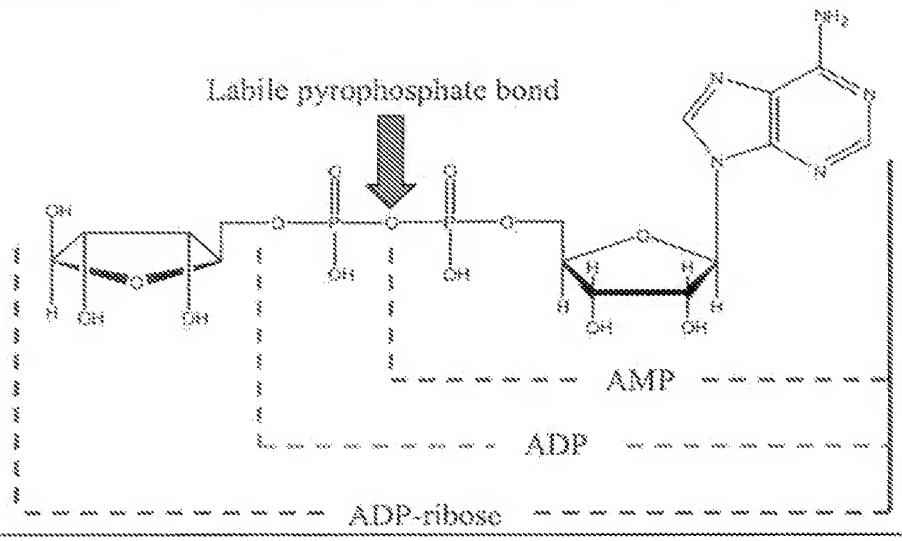

Figure 1. Structures of ADP-ribose, ADP and AMP showing the how the ADP-ribose hapten used by Bredehorst was degraded to AMP in rabbits. Note that ADP would also be expected to be degraded to AMP.

However, development of antibodies to ADP-ribose and AMP is not relevant to applicants claims, since neither ADP-ribose nor AMP is a donor product of an enzymatic group transfer reaction. The claimed invention is focused on detection of donor products produced by enzymes as indicated in Claim 1 by the phrase "in the presence of a catalytically active enzyme", and as indicated repeatedly in the specifications. Original Claim 9 and para. [0006] of the specification recite all of the group transfer enzymes that applicants are aware of, and none of them produce ADP-ribose or AMP as a product. Notably, in the case of ADP-ribosyltransferases the ADP-ribose moiety is transferred from NAD to acceptor substrates. Even in that reaction, the donor product is nicotinamide, not ADP-ribose. Since, neither ADP-ribose nor AMP is a donor product of a group transfer reaction, applicants respectfully argue that Bredehorst provides neither the teaching, the motivation nor the expectation of success for donor product detection.

One might argue that, although unintended, the development of antibodies that bind AMP selectively over ADP is equivalent to the development of antibodies that bind ADP selectively over ATP. However this is not the case because ADP contains the putatively labile pyrophosphate bond (Figure 1). Based on the results of Bredehorst, one would

conclude that the use of ADP as an immunogen would yield the same result as obtained with ADP-ribose: antibodies to AMP. In this regard, Bredehorst teaches against development of antibodies for the detection of the donor product, ADP, in the presence of ATP. Thus, Bredehorst et al. cannot be combined with other documents to establish a *prima facie* case of obviousness for the claimed embodiments.

Turning to Seethala, the Examiner appears to contradict himself repeatedly on the question of whether Seethala teaches detection of the donor product. In the initial prior office action (p. 6) it is stated that the key claims are unpatentable "over Seethala *in view of either Li et al or Glassler*." Immediately following this, it is stated that Seethala teaches "a method of detecting a donor product of a group transfer reaction", with no mention of Li et al. or Glassler. However, then the Examiner goes on to explain that in view of Li or Glassler "it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made *to modify the teaching of Seethala*……to monitor untagged ADP." It certainly appears that the Examiner is relying upon Li et al. to overcome the alleged deficiency of donor product detection in Seethala. Consistent with this line of reasoning, the Examiner acknowledges that "…Seethala does not teach detection of the donor product, ADP, by its displacement of the tagged donor product, tagged ADP."

However, in the current office action, it is again asserted that it is not necessary to combine Li with Seethala to "cure the alleged deficiency of detection of donor product such as ADP." The Examiner also asserts that Li et al., and Gassler et al. are not "relied upon to cure the alleged deficiencies of (1) *detection of donor product such as ADP*, (2) a competitive binding assay, or (3) an antibody. Seethala is relied upon for the obviousness of these three elements" (see, last paragraph of pg. 6 to top of pg. 7 of current Action).

In response, applicants continue to respectfully, yet vehemently disagree with the conclusion reached in the current Action regarding Seethala. The Examiner asserts that Seethala "teaches a method of detecting a donor product of a group transfer reaction." This is not true. To illustrate why the conclusion reached in the Action is not true, applicants reiterate below the general form for group transfer reactions:

which in the case of a kinase reaction becomes:

There are two substrates and two products. The claimed invention as amended is based on immunodetection of the donor product, ADP, in the presence of the donor, ATP, as a means of measuring kinase activity. Conversely, Seethala teaches methods for measuring kinase activity by detecting the phosphopeptide product, not the donor product.

As described in our response to the prior action, the two reaction products cannot be considered to be equivalent in the context of a kinase assay because immunodetection of phosphopeptides was common practice at the time of the invention, whereas *immunodetection of ADP was not known.* At the time of filing, there were (1) no references that described anti-ADP antibodies, (2) no commercial source available, and (3) as described in our prior response, the development of anti-ADP antibodies presented significant technical barriers.

Perhaps most importantly, and this is the essence of the claimed invention, *detection of the phosphopeptide is not a generic method, whereas detection of ADP is generic.* That is, phosphopeptide detection requires that many different reagent sets – antibodies and tracers – be developed to detect the hundreds of different phosphorylated products produced by the more than 650 kinases present in humans. Notably, several companies spent many millions of dollars developing such assays for several years after Seethala was published (Seethala originally published his method in 1997; see, Seethala, R. and R. Menzel, A homogeneous, fluorescence polarization assay for src-family tyrosine kinases. *Anal Biochem*, (1997) 253(2): p. 210-8).

In contrast, *immunodetection of ADP enables detection of any kinase, with any acceptor substrate, using the same antibody and tracer.* Once these reagents are developed, the approach of detecting many different phosphopeptides becomes obsolete. Yet, *no one conceived of applicants' elegantly simple approach in the six years following Seethala's*

original publication. Despite the millions of research and development dollars companies poured into this research because of the extremely high commercial value, there was a long time delay until applicants' developed the claimed invention (see, Dr. Lowery's Declaration under 37 CFR 1.132 filed on 01/02/2007). Applicants, thus, believe it is unreasonable to assert that because Seethala teaches detection of the phosphopeptide product of a kinase reaction, it also teaches detection of the ADP product.

Moreover, applicants' believe it is not fair to apply the disclosure of Seethala to all enzymatic reactions that form more than one product. If a detection method is disclosed for one of the products, does that make obvious the use of a similar detection method for any of the other products, regardless of the intrinsic differences in applying the method and without any consideration of the technical and utility improvements that resulted? Absolutely not!

Also, for the sake of providing a complete response, applicants reassert that Li's method does not rely on untagged adenine for "competitively displacing" tagged adenine or a nucleotide. Instead, in Li's method, the tagged adenine is enzymatically transferred to a protein where it remains covalently bound, resulting in an increase in its polarization. To adapt the method of Li for detection of kinases, one would need to use fluorescently labeled ATP as a donor molecule. This is not what applicants claim and there is nothing in the literature suggesting that such an approach would work. Moreover, the fluorescent label would need to be attached to the terminal phosphate of ATP, which would very likely affect its ability to serve as a substrate for many protein kinases. Additionally, applicants amended Claim 1 to refer to an antibody. The macromolecule in Li is not an antibody. Thus, Li discloses neither the use of a competitive binding assay for detection of ADP (nor any other nucleotide), nor that the competitive binding assay is a homogenous immunodetection assay.

Likewise, Gassler does not cure the deficiencies of Seethala or Li. Gassler does not use a homogenous immunodetection assay as the competitive binding assay (see, page 10, para. 2 of the Office Action). In Gassler, the quenching of fluorescently labeled ADP was used to monitor its rate of displacement from a protein by an excess of unlabeled ADP. The method is not being used, nor is there any suggestion of its use, for detecting ADP produced in an enzyme reaction. In fact, in the same document, they use a radioactive assay to measure the ADP formed in the ATPase enzyme reactions they are studying. Also, the binding protein in Gassler is not an antibody. Moreover, neither the Li nor Gassler methods enable

the detection of ADP in the presence of excess ATP, which is a claimed element of applicants' invention.

Therefore, it is difficult to see how one skilled in the art could reach the conclusion that the claimed invention was *prima facie* obvious based on Seethala, Li, Glasser, or Bredehorst, either alone or in combination.

In view of these remarks, applicants respectfully request that a generic claim be allowed to the applicant as the cited documents clearly do not disclose a species falling within the claimed genus (see MPEP 2131.02). Thus, a prompt and favorable consideration of this response and that a timely Notice of Allowance be issued in this case.

A Request for Continuing Examination (RCE) is enclosed herewith. Please charge this fee to Deposit Account No. 17-0055. If any other fee is due regarding this response or any other response, please consider this a request to charge the fee to Deposit Account No. 17-0055.

Respectfully submitted,

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